Genetically Engineered Mosquitoes

The mosquito… the buzzing menace of summer barbeques and campfires. While their bites may produce a mild allergic reaction in the form of irritated and bumpy skin, mosquitoes are relatively harmless throughout the United States. Globally however, mosquitoes pose a substantial health risk to millions of people due to their ability to transmit devastating illnesses, including the recently erupting Zika Virus, Dengue Fever, Yellow Fever, West Nile Virus, and, the most deadly, **Malaria**. In 2015 alone, there were over 214 million cases of malaria, causing an estimated 438,000 deaths, 70% of those being children under the age of five. The economic burden of malaria is also staggering, with UNICEF estimating that malaria slows economic growth of afflicted nations by 1.3% every year.

Malaria is caused by **Plasmodium** (small single-cell organisms in the same genus as the amoeba) parasites transmitted by female ***Anopheles* mosquitoes**. Of the four malaria-causing plasmodia, ***P. falciparum*** is the most common in Sub-Saharan Africa, where 88% of malaria cases and 91% of all malaria deaths occur. Preliminary symptoms (10-15 days after bite) include fever, headache, chills and vomiting, and are often not recognized as malaria. In adults, onset of malaria leads to a month of mono-like illness that leaves the person bedridden. In children, cases of malaria caused by *P. falciparum* are normally fatal if not treated within the first 24 hours of exhibiting symptoms. Malaria is so deadly to young children that one child dies of malaria every 30 seconds, amounting to over 3,000 per day.

For the past 18 years, the World Health Organization (WHO), partnered with UNICEF, the United Nations Development Programme, the Gates Foundation, and the World Bank, has waged a war on malaria to combat the staggering cost of human life. Due to their efforts, malaria mortality rates among populations at risk (an estimated 3.2 billion people) fell by 60% among all age groups, and 65% among children under the age of five since the year 2000. However, while 400,000 less people died from malaria in 2015 than in 2000, hundreds of thousands continue to suffer. The WHO is currently aiding governments in updating malaria elimination plans throughout the Africa Region, including Kenya. The Kenyan government is currently expressing concern over a large coastal city within its borders called Mombasa, and has asked the WHO to develop a localized plan to aid malaria prevention in the densely populated region. The WHO is considering a variety of "old school" mosquito control techniques and newly developed technologies for Mombasa. These plans are detailed below:

1. **Genetically Engineering *Anopheles* to be immune to *P. falciparum***
   Scientists can give mosquitoes genes to stop transmitting malaria. The problem is getting these anti-malaria genes into every wild mosquito. Recently scientists have developed a method using the gene-editing tool CRISPR that can give these antimalarial genes to every wild mosquito by biasing inheritance of the anti-malaria gene. Mosquitoes, like humans, have two copies of each gene – one from mom and one from dad. Normally there is a 50/50 chance that either gene will be passed on to offspring. The new CRISPR technology – called a **gene drive** - guarantees that the gene will be inherited. Over many generations, the anti-malaria gene is spread to more and more mosquitoes, until every mosquito in the population has the gene. The benefit of using a gene drive is that it would leave the wild mosquito

population intact, thus preserving ecological food chains of that region. However, as is the case with any engineered gene in wild organisms, eventually a gene drive will "break," meaning it will stop biasing its inheritance or stop killing P. falciparum. At this point, because it can no longer guarantee it's inheritance, the gene drive is subject to natural selection. Scientists know that large engineered genes are less "fit" than wild type genes, so the broken drive will be selected out of the population and will cease to exist.

2. **Sterile Insect Techniques**
   P. falciparum only resides in the guts of *female* Anopheles mosquitoes, a species of mosquito where females mate only *once in their lifetimes*. Scientists have taken advantage of this, and engineered sterile males so that when they mate with females, the females are effectively sterilized too**.** When a large number are released into the environment, the sterile males can take the place of wild type males for mating, reducing the population as females fail to produce offspring; this essentially makes the technique a chemical-free, species-specific insecticide. Unfortunately, sterile males can be less "fit" than wild type males, reducing the number of female mosquitoes they can mate with. Furthermore, reducing a local mosquito population may have negative consequences on the local ecosystem.
3. **Continuation of traditional methods**
   The statistics don't lie; since 2000, global deaths due to malaria per year have halved because of Anti-Malarial Drugs, Indoor Residual Spraying (IRS) of insecticides in houses and Long Lasting Insecticidal Nets (LLINs) around beds, as Anopheles normally feed – and spread malaria – at night. These tools have been irreplaceable in the WHO's fight against malaria, and are constantly being updated; however, because of their long history of use, both the mosquitoes and *P. falciparum* are beginning to evolve around them. Insecticide resistance has emerged in several countries, in some instances to all 4 classes of insecticides currently used. Furthermore, there have been increasing instances of Anopheles mosquitoes feeding during the day, rendering the LLINs useless. Nevertheless, these tools protect people at risk for malaria with few ecological effects.

After much consideration, the WHO has come to the decision that synthetic biologists are the best choice to help make this decision. You and your team are tasked with deciding how the WHO will proceed with their research. You and your team may choose to pursue a single route, multiple routes, and/or selecting pieces of various actions.

Some questions to keep in mind while you make your decision:

1. What are the ethical implications of releasing engineered mosquitoes?
3. At what point do environmental risks outweigh the medical risks?
4. If you were to pursue the use of genetically engineered mosquitoes, how would you consider releasing the mosquitoes? Would you perform a controlled, pilot study release in a single area? Or would you perform a large scale release to impact multiple communities?
5. The WHO, due to limited resources, has considered outsourcing components of this study to several types of organizations. These include African research institutions, university science departments, non-profit and non-governmental organizations, and private sector synthetic biology companies. How should they proceed and how should they be regulated?
6. Who should decide if the mosquitoes are released? The people? Individual African governments? The U.N.? A global scientists panel?

References

- Andie Smidler, Gene Drive Researcher at Harvard University
- WHO Malaria Factsheet (2016)
- WHO Factsheet: World Malaria Report 2015
- Alphey L., Benedict M., Bellini R., Clark G.G., Dame D.A., Serivce M.W., Dobson S.L. - Sterile- Insect Methods for Control of Mosquito-Borne Diseases: An Analysis
- CDC's "Chapter 3: Infectious Diseases Related to Travel" Factsheet
- WHO Dengue and Severe Dengue Factsheet (2016)
- UNICEF's "The Reality of Malaria" factsheet
- WHO's "Global Technical Strategy for Malaria: 2016-2030" (2015)
- Abdoulaye Diabate and Frédéric Tripet - Targeting male mosquito behavior for malaria control
- Boston's Museum of Science "Should we Engineer the Mosquito?"

Group Planning Sheet

1. **Should we release genetically engineered mosquitoes? Why or why not?**

2. **If so, who should be in charge and how should they go about releasing mosquitoes?**

3. **What are the three greatest obstacles in implementing your plan, and how do you think synthetic biology could be used to overcome these obstacles?**

4. **A large minority of the population is concerned with the ethical implications of your plan. What ethical issues are evident in your plan, and how can you address these issues to ease the concerns of the public?**